

5 **WHAT IS CLAIMED IS:**

1. A method of treating or reducing the risk of acquiring osteoporosis comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 β ,17 β -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

15 2. A method of treating or reducing the risk of acquiring hypercholesterolemia comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 β ,17 β -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

25 3. A method of treating or reducing the risk of acquiring hyperlipidemia comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 β ,17 β -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

30

5

4. A method of treating or reducing the risk of acquiring atherosclerosis comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 β ,17 β -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

15

5. A method of treating or reducing the risk of acquiring breast cancer comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 β ,17 β -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

20

6. A method of treating or reducing the risk of acquiring endometrial cancer comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate and androst-5-ene-3 β ,17 β -diol , in a patient in need of said treatment or said reduction, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

25

30

5 7. A method of treating or reducing the risk of acquiring
uterine cancer comprising increasing levels of a sex steroid precursor
selected from the group consisting of dehydroepiandrosterone,
dehydroepiandrosterone-sulfate and androst-5-ene-3 β ,17 β -diol , in a
patient in need of said treatment or said reduction, and further
10 comprising administering to said patient a therapeutically effective
amount of a selective estrogen receptor modulator as part of a
combination therapy.

15 8. A method of treating or reducing the risk of acquiring
ovarian cancer comprising increasing levels of a sex steroid precursor
selected from the group consisting of dehydroepiandrosterone,
dehydroepiandrosterone-sulfate and androst-5-ene-3 β ,17 β -diol , in a
patient in need of said treatment or said reduction, and further
comprising administering to said patient a therapeutically effective
20 amount of a selective estrogen receptor modulator as part of a
combination therapy.

25 9. The method of claim 1 further comprising the step of
administering a therapeutically effective amount of a bisphosphonate as
part of said combination therapy.

30 10. A kit comprising a first container containing a
therapeutically effective amount of at least one sex steroid precursor
selected from the group consisting of dehydroepiandrosterone,
dehydroepiandrosterone-sulfate, androst-5-ene-3 β ,17 β -diol and any
prodrug that is converted in vivo any into the foregoing precursors; and

5 further comprising a second container containing a therapeutically effective amount of at least one selective estrogen receptor modulator .

11. A pharmaceutical composition comprising:

a) a pharmaceutically acceptable excipient, diluent or carrier;

10 b) a therapeutically effective amount of at least one sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3 β ,17 β -diol and a prodrug that is converted *in vivo* into any of the foregoing sex steroid precursors; and

15 c) a therapeutically effective amount of at least one selective estrogen receptor modulator .

20 12. A kit of claim 10 comprising at least one additional container of said kit that contains a therapeutically effective amount of at least one bisphosphonate.

25 13. A pharmaceutical composition of claim 11 wherein said composition further comprising a therapeutically effective amount of at least one bisphosphonate.

14. The method of claim 1 further comprising administering a therapeutically effective amount of a progestin.

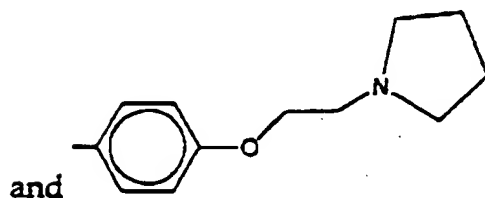
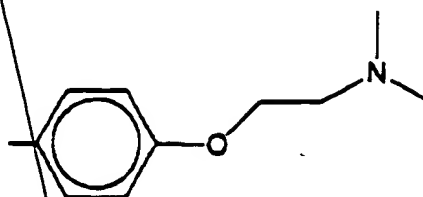
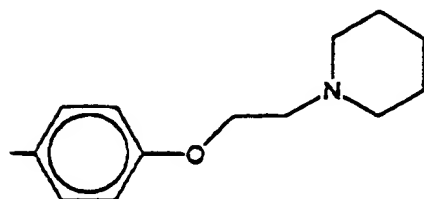
30 15. The method of Claim 1 wherein the selective estrogen receptor modulator has a molecular formula with the following features :

a) two aromatic rings spaced by 1 to 2 intervening carbon atoms, both aromatic rings being either unsubstituted or

5 substituted by a hydroxyl group or a group converted *in vivo* to hydroxyl;

b) a side chain possessing an aromatic ring and a tertiary amine function or salt thereof.

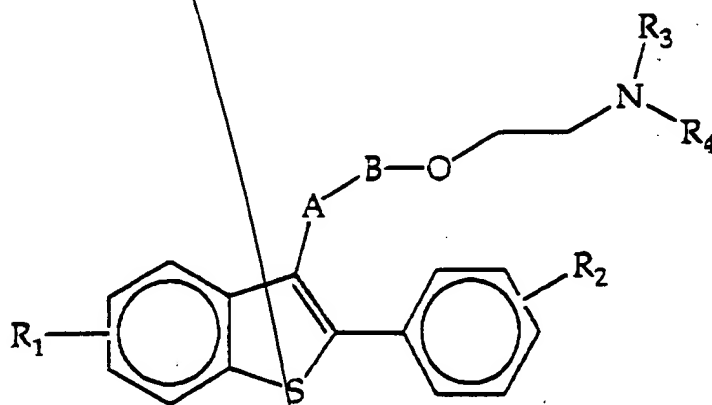
10 16. A method of Claims 15 wherein the side chain is selected from the group consisting of :



15 17. The method of Claim 15 wherein the two aromatic rings are both phenyl and wherein the side chain possesses a moiety selected from the group consisting of a methine, a methylene, -CO, -O-, and -S-, an aromatic ring, and a tertiary amine function or salt thereof

20 18. The method of Claim 15 wherein the selective estrogen receptor modulator is selected from the group consisting of a benzothiophene derivative, triphenylethylene derivative, indole derivative, benzopyran derivative, and centchroman derivative.

5 19. The method of Claim 15 wherein the selective estrogen receptor modulator is a benzothiophene derivative compound of the following formula:



10 wherein R₁ and R₂ are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl ;

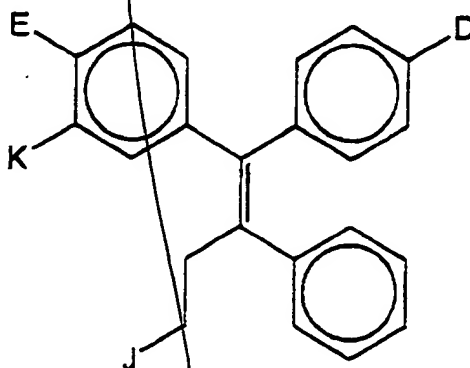
 wherein R₃ and R₄ are either independently selected from the group consisting of : C1-C4 alkyl, or wherein R₃, R₄ and the nitrogen to which they are bound, together are any structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino;

 wherein A is selected from the group consisting of -CO-, -CHOH, and -CH₂-;

20 wherein B is selected from the group consisting of phenylene, pyridylidene, and -cycloC₄H₂N₂-.

25 20. The method of Claim 19 wherein the selective estrogen receptor modulator is selected from the group consisting of Raloxifene, LY 353381 and LY 335563.

5 21. The method of Claim 15 wherein the selective estrogen receptor modulator is a triphenylethylene derivative compound of the following formula :



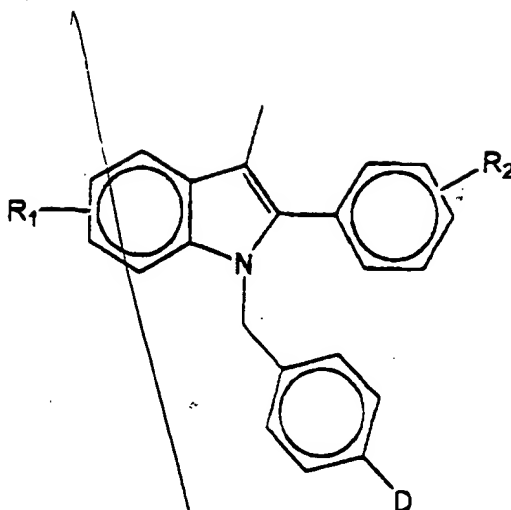
10 wherein D is -OCH₂CH₂N(R₃)R₄ or -CH=CH-COOH (R₃ and R₄ either being independently selected from the group consisting of C1-C4 alkyl, or R₃, R₄, and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1- pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino and morpholino);

15 wherein E and K are independently hydrogen or hydroxyl;

 wherein J is hydrogen or halogen.

20 22. The method of claim 12 wherein selective estrogen receptor modulator is Tamoxifen, OH-tamoxifen, Droloxifene, Toremifene, Iodoxifene, and GW5638.

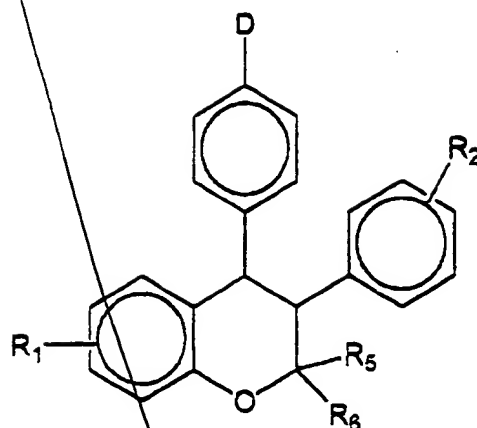
25 23. The method of Claim 15 wherein the selective estrogen receptor modulator is an indole derivative compound of the following formula:



5
10
wherein D is $-OCH_2CH_2N(R_3)R_4$ (R_3 and R_4 either being independently selected from the group consisting of C_1 - C_4 alkyl, or R_3 , R_4 and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring).

15
wherein R_1 and R_2 are independently selected from the group consisting of : hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl.

24. The method of Claim 15 wherein the selective estrogen receptor modulator is a centchroman derivative compound of the following formula :



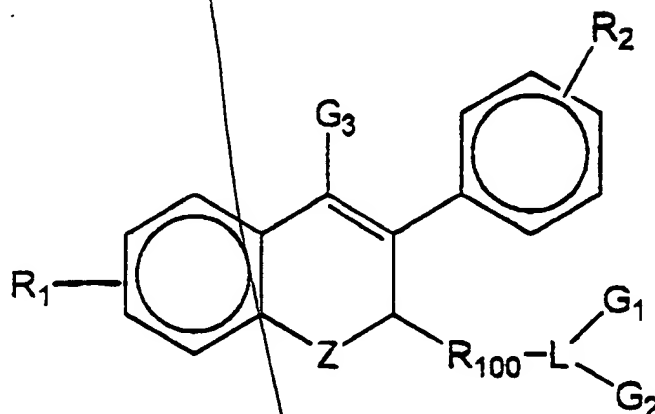
wherein R_1 and R_2 are independently selected from the group consisting of: hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl;

wherein R_5 and R_6 are independently hydrogen or C_1 - C_6 alkyl;

wherein D is $-OCH_2CH_2N(R_3)R_4$ (R_3 and R_4 either being independently selected from the group consisting of C_1 - C_4 alkyl, or R_3 , R_4 and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring).

25. The method of Claim 24 wherein the centchroman derivative is (3,4-trans-2,2-dimethyl-3-phenyl-4-[4-(2-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-7-methoxychroman).

26. The method of Claim 15 wherein the selective estrogen receptor modulator has the following formula :



wherein R₁ and R₂ are independently hydrogen, hydroxyl or a moiety which is converted to hydroxyl in vivo ;

wherein Z is a bivalent closing moiety ;

wherein the R₁₀₀ is a bivalent moiety which distances L from the B-ring by 4-10 intervening atoms ;

wherein L is a bivalent or trivalent polar moiety selected from the group of -SO-, -CON-, -N<, and -SON< ;

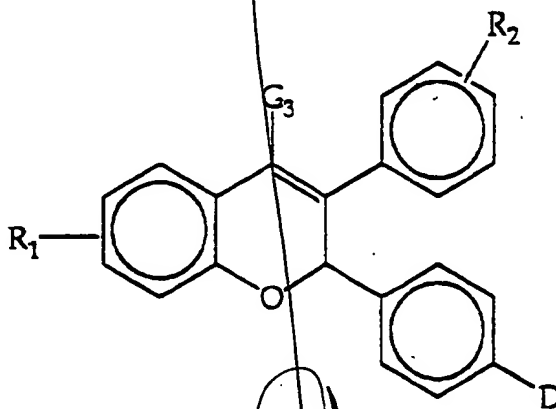
wherein G₁ is selected from the group consisting of hydrogen, a C₁ to C₅ hydrocarbon or a bivalent moiety which joins G₂ and L to form a 5- to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing.

wherein G₂ is either absent or selected from the group consisting of hydrogen, a C₁ to C₅ hydrocarbon or a bivalent moiety which joins G₁ and L to form a 5- to 7- membered heterocyclic ring, and halo or unsaturated derivatives of the foregoing.

wherein G₃ is selected from the group consisting of hydrogen, methyl and ethyl.

5 27. The method of Claim 26, wherein Z is selected from the group consisting of -O-, -NH-, -S-, and -CH₂-.

28. The method of Claim 27, wherein the compound is a benzopyran derivative of the following general structure :

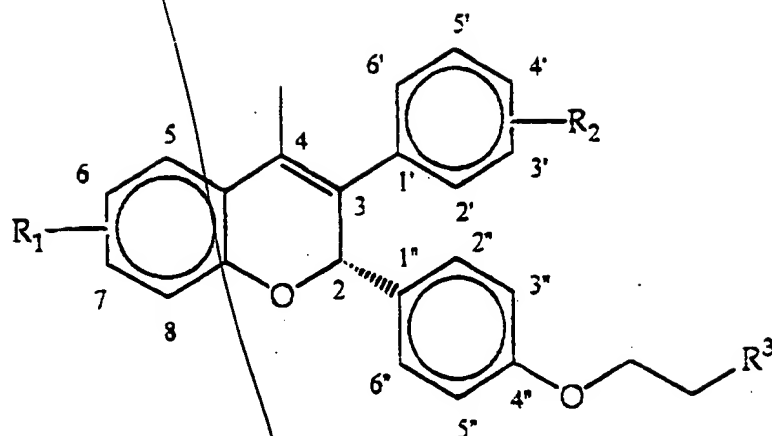


10 wherein D is -OCH₂CH₂N(R₃)R₄ (R₃ and R₄ either being independently selected from the group consisting of C₁-C₄ alkyl, or R₃, R₄ and the nitrogen atom to which they are bound, together being a ring structure selected from the group consisting of pyrrolidino, dimethyl-1-pyrrolidino, methyl-1-pyrrolidinyl, piperidino, hexamethyleneimino, morpholino, ring).

15 wherein R₁ and R₂ are independently selected from the group consisting of: hydrogen, hydroxyl, and a moiety converted in vivo in hydroxyl.

20 29. The method of Claim 28, wherein the benzopyran derivative is an optically active compound having an absolute configuration S on carbon 2 or pharmaceutically acceptable salt thereof, said compound having the molecular structure:

25



wherein R_1 and R_2 are independently selected from the group consisting of hydroxyl and a moiety convertible *in vivo* to hydroxyl;

wherein R^3 is a species selected from the group consisting of saturated, unsaturated or substituted pyrrolidinyl, saturated, unsaturated or substituted piperidino, saturated, unsaturated or substituted piperidinyl, saturated, unsaturated or substituted morpholino, nitrogen-containing cyclic moiety, nitrogen-containing polycyclic moiety, and $NRaRb$ (Ra and Rb being independently hydrogen, straight or branched C_1-C_6 alkyl, straight or branched C_2-C_6 alkenyl, and straight or branched C_2-C_6 alkynyl).

30. The method of claim 29 wherein said compound or salt substantially lacks (2R)-enantiomer.

31. The method of claim 28 where said selective estrogen receptor modulator is selected from the group consisting of:

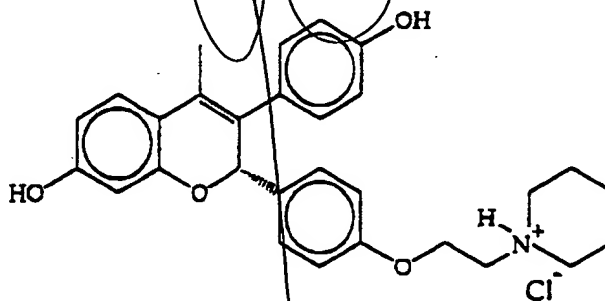
CC1=C(C2=CC=CC=C2C(=O)OCCN3CCCCC3)C(=C(C4=CC=CC=C4C(=O)OCC5CCCCC5)C1=C(C6=CC=CC=C6C(=O)OCC7CCCCC7)C2=CC=CC=C6C(=O)OCC8CCCCC8)C3=CC=CC=C3C(=O)OCC9CCCCC9CCOC(=O)c1ccc(cc1)C2=C(C(=C3C=C(C=C(C=C3)OC)O)C=C2c4ccc(cc4)OCCCN5CCCCC5)c6ccc(cc6)OC(=O)CCCOC(=O)c1ccc(cc1)C2=C(C(=O)OCCN3CCCCC3)OC(c4ccccc4)C2C(=O)OCC(=O)c5ccccc5CCOC(=O)c1ccc2c(c1)oc3c2c4ccc(OC(=O)CC)cc4c5ccc(OC(=O)CCN6CCCCC6)cc53[illegible]

5 32. The method of claim 29 wherein the benzopyran derivative
is a salt of an acid selected from the group consisting of acetic acid, adipic
acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric
acid, fumaric acid, hydroiodic acid, hydrobromic acid, hydrochloric acid,
hydrochlorothiazide acid, hydroxy-naphthoic acid, lactic acid, maleic
10 acid, methanesulfonic acid, methylsulfuric acid, 1,5-
naphthalenedisulfonic acid, nitric acid, palmitic acid, pivalic acid,
phosphoric acid, propionic acid, succinic acid, sulfuric acid, tartaric acid,
terephthalic acid, p-toluenesulfonic acid, and valeric acid.

15 33. The method of claim 32 wherein the acid is hydrochloric
acid.

 34. The method of claim 1 wherein said selective estrogen
receptor modulator is:

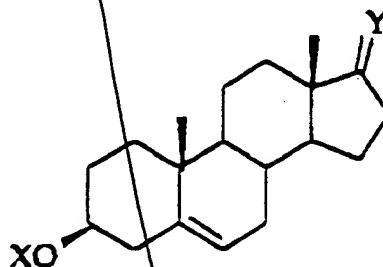
EM-1538



20 and an amount of a sex steroid precursor selected from the group
consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate,
androst-5-ene-3 β ,17 β -diol.

25 35. The method of claim 1 wherein the sex steroid precursor is
dehydroepiandrosterone.

5 36. The method of claim 1 wherein the compound converted *in vivo* to into sex steroid precursor has the general formula :



10 wherein X is selected from the group consisting of H- , ROC-,
RCO₂CHRa- and RbSO₂- (R being selected from the group consisting of
hydrogen, straight- or branched-(C₁-C₁₈) alkyl, straight- or branched-(C₂-
C₁₈) alkenyl, straight- or branched-(C₂-C₁₈) alkynyl, aryl, furyl, straight-
or branched-(C₁-C₁₈) alkoxy, straight- or branched-(C₂-C₁₈) alkenyloxy,
15 straight- or branched-(C₂-C₁₈) alkynyloxy, aryloxy, furyloxy, and
halogeno or carboxyl analogs of the foregoing; Ra being hydrogen or
(C₁-C₆) alkyl; and, Rb being selected from the group consisting of
hydroxyl (or salts thereof), methyl, phenyl and p-toluyyl);

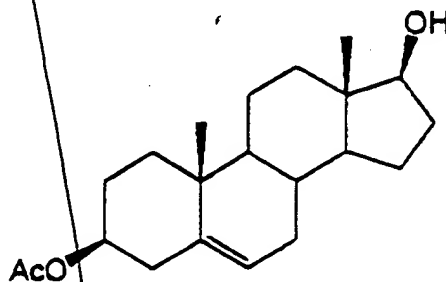
20 wherein Y is carbonyl oxygen or Y represent a β-OX (X having the
same meaning as above) and α-H.

- 93 -

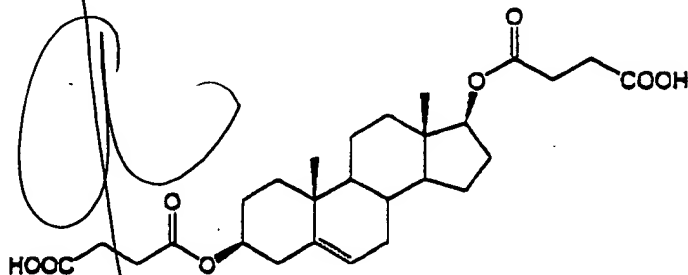
5

37. The method of claim 1 wherein the compound converted *in vivo* to into sex steroid precursor is selected from the group consisting of :

EM-1304



EM-01474-D



10

38. The method of claim 1, further comprising administering a therapeutically effective amount of a progestin.

ADD
21